

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/100339 A2

- (51) International Patent Classification⁷: **A61K**
- (21) International Application Number: PCT/US02/18329
- (22) International Filing Date: 13 June 2002 (13.06.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/298,009 13 June 2001 (13.06.2001) US
60/371,069 9 April 2002 (09.04.2002) US
- (71) Applicant (for all designated States except BB, US): **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 3190, 49131 Petah Tiqva (IL).
- (71) Applicant (for BB only): **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **DOLITZKY, Ben-Zion** [IL/IL]; Lochamei Hageittaot 32, Petach Tikva (IL). **REANY, Ofer** [IL/IL]; House No. 70, Chitim Village, Lower Gallilee, 15280 Israel (IL). **SHAMAI, Jenny** [IL/IL]; Kiryat Yam, 15280 Israel (IL).
- (74) Agents: **BRAINARD, Charles, R.** et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/100339 A2

(54) Title: NOVEL PROCESS FOR PREPARING RAC-BICALUTAMIDE AND ITS INTERMEDIATES

(57) Abstract: The present invention relates to a new process for the synthesis of racemic and optically active bicalutamide starting from ethyl pyruvate and methyl methacrylate. The present invention discloses processes of preparing bicalutamide intermediates including ethyl-[2-(4-fluorophenyl sulfone)]-2-hydroxy propionate, 1,2-epoxy-2-methyl propionate and 2-hydrox-2-methyl-3-(4-fluorophenylthio) propionic acid. The present invention further discloses micronized *rac*-bicalutamide and the preparation thereof.

NOVEL PROCESS FOR PREPARING *RAC*-BICALUTAMIDE AND ITS INTERMEDIATES

CROSS REFERENCE TO RELATED APPLICATIONS

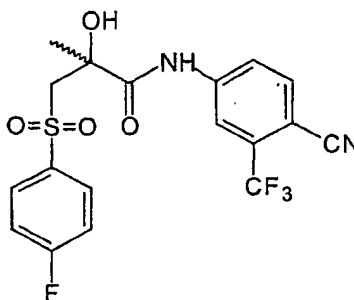
5 This application claims the benefits under 35 U.S.C. § 119(e) of Provisional Application Serial Nos. 60/298,009, filed June 13, 2001 and 60/371,069, filed on April 9, 2002, the disclosures of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

10 The present invention relates to process for preparing *rac*-bicalutamide and its intermediates. The prevent invention also relates to micronized *rac*-bicalutamides and their preparations thereof.

BACKGROUND OF THE INVENTION

15 Bicalutamide is also known as N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide and has the following chemical formula.



Bicalutamide

25 Bicalutamide is an acylanilid that has anti-androgen activity. It is known to selectively decrease the testosterone level without influencing the regulation mechanisms of the hypothalamus.

30 The international patent No. WO 93/19770 describes both R-(-) enantiomer and S-(+) enantiomer for bicalutamide, of which the R-(-) isomer is reported to be more active and possesses lesser side-effects (e.g., headache, gynecomastia and giddiness) when used in therapy treatment.

U.S. Pat. No. 4,636,505 describes processes for preparing acylanilides.

The international Pat. No. WO 01/00608 describes a process for racemic and optically pure N-[4-cyano-3-trifluoromethylphenyl]-3-[4-fluorophenyl-sulfonyl]-2-
5 hydroxy-2-methyl-propionamide. The process involves multiple steps including at least reacting with thionyl chloride; hydrolyzing under aqueous basic conditions; sulfonylating with sulfonyl halogenide; and oxidizing with inorganic peroxy salt, or m-chloroperbenzoic acid (MCPBA) or aqueous hydrogen peroxide. However, the synthetic pathways involve the use of substrates (such as sodium hydride) that are dangerously explosive in nature.

10

There is a constant need to improve the synthesis process for bicalutamide which are economical and environmental safe and feasible.

We have now found a simpler method of preparing bicalutamide and its
15 intermediates without using dangerous oxidizing compounds such as m-chloroperbenzoic acid.

OBJECTS AND SUMMARY OF THE INVENTION

The present invention provides new synthetic pathways for preparing *rac*-
20 bicalutamide and its intermediates.

According to one object, the present invention is directed to a *rac*-bicalutamide intermediate having a chemical formula of [X], which represents a stable organo lithium salt of 4-fluorophenyl methyl sulfone.

25

According to another object, the present invention is directed to a process of preparing [X], comprising the step of reacting 4-fluorophenyl methyl sulfone with butyl lithium to form the organo lithium salt of 4-fluorophenyl methyl sulfone.

30

According to another object, the present invention provides a novel process for preparing *rac*-ethyl 1-[2-{4-fluorophenyl sulfone}] -2-hydroxy propionic acid, comprising the step of reacting the organo lithium salt of 4-fluorophenyl methyl sulfone with ethyl pyruvate.

According to another object, the present invention is directed to a *rac*-bicalutamide intermediate having a chemical formula of [Y], which represents a stable lithium salt of 5-amino-2-cyano-benzotrifluoride.

5

According to another object, the present invention provides a process for preparing [Y], comprising the step of reacting 5-amino-2-cyano-benzotrifluoride with butyl lithium to form the lithium salt of 5-amino-cyano-benzotrifluoride.

10

According to another object, the present invention provides a process for preparing *rac*-bicalutamide, comprising the step of reacting [Y] with *rac*-ethyl 1-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid.

According to another object, the present invention provides a process for preparing *rac*-ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid, comprising the steps of:

15

- 1) mixing 4-fluorophenyl methyl sulfone with butyl lithium to obtain an intermediate having a chemical structure [X];
- 2) adding ethyl pyruvate; and
- 3) recovering *rac*-ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid.

20

Preferably, 1,4 diazabicyclo[2.2.2]octane in tetrahydrofuran is used as a stabilized agent in step 1.

25

According to another object, the present invention provides a process for preparing *rac*-bicalutamide comprising the steps of:

30

- 1) mixing 5-amino-2-cyano-benzotrifluoride and butyl lithium to obtain a lithium salt of 5-amino-2-cyano-benzotrifluoride;
- 2) adding *rac*-ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid; and
- 3) recovering *rac*-bicalutamide.

Preferably, the step 1) is occurred in the presence of 1,4 diazabicyclo[2.2.2]octane in tetrahydrofuran.

According to one object, the present invention provides a novel process of preparing micronized forms of *rac*-bicalutamide.

5 According to another object, the present invention provides a synthesis process of preparing *rac*-bicalutamide with a particle size in which the mean particle size enhances the rate of dissolution and the reproducibility of dissolution. The present invention provides *rac*-bicalutamide in which the mean particle size imparts an improved and stable dissolution profile.

10 According to another object, the present invention provides *rac*-bicalutamide formulations containing *rac*-bicalutamide having relatively small particles, and corresponding large surface area.

15 According to another object, the present invention provides *rac*-bicalutamide with a particle size which enhances the rate of dissolution and the reproducibility of the rate of dissolution.

20 According to another object, the present invention provides *rac*-bicalutamide in which the mean particle size imparts an improved and stable dissolution profile.

According to another object, the present invention provides *rac*-bicalutamide and formulations containing *rac*-bicalutamide having a mean particle diameter of less than 200 μm .

25 According to another object, the present invention provides a process for preparing micronized *rac*-bicalutamide.

According to another object, the present invention provides pharmaceutical compositions comprising micronized *rac*-bicalutamide.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 depicts the reaction pathway of *rac*-bicalutamide synthesis starting from ethyl pyruvate.

5

Fig. 2 depicts the reaction pathway of *rac*-bicalutamide synthesis starting from methyl methacrylate.

DETAILED DESCRIPTION OF THE INVENTION

10 Definitions:

As used herein, *rac*-bicalutamide refers to both the R-(-) enantiomer and S-(+) enantiomer of bicalutamide. *Rac*-bicalutamide is the racemic and optically pure R-(-) and S-(+) isomers of N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide. It is to be understood that this invention encompasses
15 the racemic form of bicalutamide and any optically-active form which possesses anti-androgenic activity. It is a matter of common general knowledge how a racemic compound may be resolved into its optically-active forms and how any anti-androgenic activity present in any of these forms may be determined. One skilled in the art will appreciate that the separation of optical isomers can be achieved by conventional
20 resolution; such as fractional crystallization or flash-chromatography.

As used herein, the term "micronized" refers to particles having a mean particle diameter of less than about 200 μm .

25 As used herein, the term " μm " refers to "micrometer" which is 1×10^{-6} meter.

The following abbreviations are used herein: DCM is dichloromethane. THF is tetrahydrofuran. DABCO is 1,4 dizazabicyl [2.2.2] octane. ACB is 5-amino-2-cyano-benzotrofluoride. BCL is *rac*-bicalutamide. 4-FPMS is 4-fluorophenyl methyl sulfone.

30

The present invention provides a novel process for preparing *rac*-bicalutamide from ethyl pyruvate and 4-fluorophenyl methyl sulfone via the formation of an intermediate with chemical formula of [X].

The present invention further provides a novel process for preparing *rac*-bicalutamide from 4-fluorophenyl methyl sulfone. Butyl lithium reacts with 4-fluorophenyl methyl sulfone with a base to form an organo lithium the intermediate (i.e.,
5 with chemical formula of [X]), optionally in the presence of anion stabilizer such as DABCO. The base refers to strong bases such as lithium diisopropyl amid (LDA) or its derivatives. This reaction is preferably carried out in an inert organic solvent, for example tetrahydrofuran or diethyl ether. Most preferable solvent is tetrahydrofuran. The reaction is preferably carried out at a low temperature, for example -40°C to 10°C . Most
10 preferable temperature is between -2°C and 2°C .

Figure 1 illustrates the schematic process for preparing *rac*-bicalutamide from ethyl pyruvate and 4-fluorophenyl methyl sulfone. The intermediate with general chemical formula of [X] reacts with ethyl pyruvate to form ethyl-[2-4-{4-fluorophenyl
15 sulfone}]-2-hydroxy propionate. This reaction is preferably carried out in an inert organic solvent, for example tetrahydrofuran or diethyl ether. Most preferable solvent is tetrahydrofuran. The reaction is preferably carried out at a low temperature, for example -60°C to -100°C . Most preferable temperature is -60°C .

20 The present invention provides a process of preparing *rac*-bicalutamide from 5-amino-2-cyano-benzotrifluoride. Butyl lithium reacts with 5-amino-2-cyano-benzotrifluoride with a base to form an organo lithium the intermediate (i.e., with chemical formula of [Y]), optionally in the presence of anion stabilizer such as DABCO. The base refers to strong bases such as lithium diisopropyl amid (LDA) or its derivatives.
25 This reaction is preferably carried out in an inert organic solvent, for example tetrahydrofuran or diethyl ether. Most preferable solvent is tetrahydrofuran. The reaction is preferably carried out at a low temperature, for example -40°C to 10°C . Most preferable temperature is between -2°C and 2°C .

The present invention provides a process of preparing *rac*-bicalutamide from 5-amino-2-cyano-benzotrifluoride via intermediate with chemical formula of [Y].
30 Intermediate with chemical formula [Y] thus formed reacts with *rac*-ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionate to form *rac*-bicalutamide. This reaction is

preferably carried out in an inert organic solvent, for example tetrahydrofuran or diethyl ether. Most preferable solvent is tetrahydrofuran. The reaction is preferably carried out at a low temperature, for example -60°C to -100°C . Most preferable temperature is -60°C .

5 The detailed procedures of preparing *rac*-ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid from ethyl pyruvate and 4-fluorophenyl methyl sulfone as well as *rac*-bicalutamide from *rac*-ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid and 5-amino-2-cyano-benzotrifluoride are illustrated in Fig. 1.

10 The process according to our invention is described in detail by the following, but not limiting, examples.

Example 1

Preparation of *rac*-Ethyl-[2-{4-Fluorophenyl Sulfone}]-2-Hydroxy Propionate

15 4-Fluorophenyl methyl sulfone (4-FPMS) (5 grams, 27.8 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO) (3.2 grams, 28.5 mmol) were dissolved in tetrahydrofuran (THF) and cooled in dry-ice acetone bath to about -2°C .

20 A 2.5 M solution of butyl lithium in hexanes (14.5 mL, 36.2 mmol) was added to the cold THF solution dropwise via a syringe while keeping the temperature between about -2°C to about 2°C . After addition was completed the stirring was continued for about 1 hour while maintaining the temperature at about -2°C . Then, the temperature was lowered to about -65°C and a solution of ethyl pyruvate (3.67 grams, 31.6 mmol) in THF
25 (30 mL) was added dropwise.

 After addition was completed, the stirring was continued for an hour at temperatures between about -65°C and about -30°C and then followed by an addition of 2N HCl (30 mL) dropwise to the reaction mixture at about -30°C . The reaction was
30 allowed to warm-up to room temperature and the mixture was evaporated in vacuo on a rotary evaporator to remove THF and ethanol.

The residual material was extracted with diethyl ether (3×100 mL). The combined ether extracts were dried over Na₂SO₄, filtered and the filtrate was completely evaporated to give a crude oil.

5 The product was purified by column chromatography on silica gel via eluting with dichloromethane (DCM) to give *rac*-ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionate as colorless oil.

The purified product was characterized by a ¹H NMR (500 MHz, CDCl₃): 7.92 (m, 10 2H), 7.22 (m, 2H), 4.29 (m, 2H, OCH₂), 3.77 (d, *J*=15 Hz, 1H, CH_{2α}), 3.68 (bs, 1H, OH), 3.55 (d, *J*=15 Hz, 1H, CH_{2β}), 1.45 (s, 3H, Me), 1.35 (t, *J*=7 Hz, 3H, OCH₂CH₃).

The purified product was further characterized by a ¹³C NMR (125.7 MHz, CDCl₃): 174.7 ppm (CO_{ester}), 166.4 (C-4', *J*_{C-F}=258 Hz), 137.5 ((c-1')), 131.7 (C-2',6', *J*_{C-F}=9 Hz), 117.0 (C-3',5', *J*_{C-F}=21.6 Hz), 72.9 (C_{quat}), 64.6 (CH₂), 63.6 (OCH₂), 27.9 (CH₃), 14.7 (OCH₂CH₃). 15

The purified product was further characterized by HPLC (acetonitrile:water 1:1 with 0.01% TFA): 5.4 mins.

20

Example 2

Preparation of *rac*-N-[4-Cyano-3-Trifluoromethyl-Phenyl]-3-[4-Fluorophenyl Sulfonyl]-2-Hydroxy-2-Methyl-Propionamide

25 5-Amino-2-cyano-benzotrifluoride (ACB) (0.27 grams, 1.45 mmol) and 1,4 diazabicyclo[2.2.2]octane (DABCO) (0.32 grams, 2.85 mmol) were dissolved in tetrahydrofuran (THF) (30 mL) and cooled in dry-ice acetone bath to about -2 °C.

A 2.5M solution of butyl lithium in hexanes (2 mL, 5 mmol) was added to the cold 30 THF solution dropwise via a syringe while keeping the temperature between about -2 to about 2 °C. After addition was completed, the stirring was continued for 1 hour while maintaining the temperature at about -2 °C. The temperature was then lowered to about -

65 °C and a solution of *rac*-Ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionate (0.34 grams, 1.17 mmol) in THF (20 mL) was added dropwise.

After addition was completed, the stirring was continued for an hour at
5 temperatures between about -65°C and about -30°C after which 2N HCl (30 mL) was added dropwise to the reaction mixture at about -30 °C. The reaction was allowed to warm-up to room temperature and the mixture was evaporated in vacuo on a rotary evaporator to remove THF and ethanol.

10 The residual material was extracted with diethyl ether (3×100 mL). The combined ether extracts were dried over Na₂SO₄, filtered and the filtrate was completely evaporated to give a crude oil.

The product was purified by column chromatography on silica gel eluting with
15 ethyl acetate – petroleum ether to give *rac*-N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl sulfonyl]-2-hydroxy-2-methyl- propionamide in about 40% yield, as a pale yellow solid.

The present invention further provides a novel process for preparing *rac*-
20 bicalutamide from methyl methacrylate. Fig. 2 illustrates the schematic process for preparing *rac*-bicalutamide from methyl methacrylate.

According to Fig. 2, the starting material was methyl methacrylate, which can usually be converted into the epoxide only under harsh conditions (i.e. with *peracetic acid*
25 in ethyl acetate at 75°C [J.A.Chem., 81, 680 (1959)], or with 90% hydrogen peroxide-trifluoroacetic anhydride at 40°C [J.Am.Chem., 77, 89 (1955)], or with MCPBA in dichloromethane at 0°C in low yield [J.Med.Chem., 29, 2184 (1986)]. The epoxidation under these conditions can be explosive. The present invention describes this oxidation using Oxone®.

30

The methyl 2-methyl-oxirane-carboxylate of formula (1), which was obtained by epoxidation, was reacted with 4-fluorothiophenol [formula (2)] in the presence of sodium

hydride under the conditions listed in Scheme-2. The obtained methyl 2-hydroxy-2-methyl-3-(4-fluorophenylthio)-propionate of formula (3) was hydrolyzed with potassium hydroxide in aqueous ethanol over a period of 22 hours to yield the 2-hydroxy-2-methyl-3-(4-fluorophenylthio)-propionic acid of formula (4), which was converted into the acid chloride of formula (5) with thionyl chloride in dimethyl acetamide at -15°C .

The obtained acid chloride was reacted with 4-amino-2-trifluoromethyl-benzonitrile in dimethylacetamide at -15°C to yield the thioether derivative of formula (6). The oxidation of the thioether derivative was carried out by known method with m-chloroperbenzoic acid in dichloromethane to yield the final product, bicalutamide, of formula (7).

The process according to our invention is described in detail by the following, but not limiting, examples.

15

Example 3

Preparation of Methyl 1,2-Epoxy-2-Methyl-Propionate

In a 3L four-neck round bottom flask, Oxone[®] (50% KHSO_5 , 227 grams, 0.75 mol) was dissolved in water (1L) and 10 M KOH was added to adjust the pH to ~ 6 (~ 53 mL). Then, methyl methacrylate (13 mL, 0.122 mol) in methanol was added (50 mL) followed by 360 mL of water.

The solution was stirred at room temperature and the pH was continuously adjusted to pH = 6 with 1M KOH (~ 270 mL). After 6 hr the reaction was stirred over night. Then, 2N HCl was added (100 mL, pH=3) and the entire aqueous solution was extracted with DCM (3×150 mL) for each 400 mL reaction solution. The combined DCM extracts were washed with saturated sodium sulfite solution followed by saturated sodium bicarbonate solution.

30

After drying and filtration, DCM was removed by evaporation and the unreacted methyl methacrylate was distilled out. The residue contained the product as an oily material.

5 GC: (>97%, 1.45 min); yield: 66%; ^1H NMR (500 MHz, CDCl_3 ; δ ppm 3.72 (s, 3H, Me), 3.07 (dd, $J=6$ Hz, $J=16$ Hz, 1H, H_O), 2.73 (d, $J=6$ Hz, 1H, H_O), 1.55 (s, Me); ^{13}C -NMR (125.7 MHz, CDCl_3 ; δ ppm): 172 (CO_ester), 54.3 (CH_2), 53.6 (C_quat), 53.2 (Me_ester), 18 (Me).

10

Example 4

Preparation of 2-Hydroxy-2-Methyl-3-(4-Fluorophenylthio) Propionic Acid

To a solution of 4-fluorothiophenol (1 mL) in MeOH (32 mL) was added dropwise 2N NaOH_aq . (16 mL) under N_2 , while the temperature was kept at 25°C during the addition
15 period. When addition was completed, the reaction mixture was stirred at room temperature for a further 90 min.

A solution of methyl-1,2-epoxy-2-methyl propionate (1.2 gram) in MeOH (20 mL) was then added dropwise at room temperature. When addition was completed, the
20 reaction mixture was stirred over night at ambient temperature. To the reaction mixture 2N HCl (20 mL) was added followed by ethyl acetate (60 mL). The organic phase was separated. The aqueous phase (pH~2) was extracted with 60 mL of chloroform and then discarded. The ethyl acetate and chloroform extracts were combined.

25 After drying (MgSO_4) and filtration, the two organic solvents were evaporated to leave an oily product which solidified upon standing at room temperature.

Purity: 75% (according to GC); Yield: 66%. GCMS: 230 m/z (13%); M.p.: 69.1 - 72.7°C ; ^1H NMR (500 MHz, CDCl_3 ; δ ppm 7.43 (m, 2H, H-2',6'), 6.96 (m, 2H, H-3',5'), 3.39 (d, $J=14$ Hz, 1H, H_O), 3.17 (d, $J=14$ Hz, 1H, H_O), 1.53 (s, Me); ^{13}C -NMR
30 (125.7 MHz, CDCl_3 ; δ ppm): 180.4 (CO_acid), 162.6 (d, $J_{\text{C-F}} = 248$ Hz, C-4'), 134.3 (d, $J_{\text{C-}}$

$f=7.5$ Hz, C-2',6'), 130.8 (d, $J_{C-F} = 3.2$ Hz, C-1'), 116.5 (d, $J_{C-F} = 21.6$ Hz, C-3',5'), 75.2 (C_{quat}), 53.3 (Me_{ester}), 46.4 (CH₂), 26.0 (Me).

5

MICRONIZED *RAC*-BICALUTAMIDE

The Particle Size Distribution (PSD) of *rac*-bicalutamide may be used to determine the available surface area for the drug dissolution. Often, it is observed that the available surface area for drug dissolution correlates to both (a) the rate of dissolution and solubility where a great surface area enhances the solubility of a drug; and (b) enhances the rate of dissolution of a drug. The rate of dissolution of a drug effects the drug's bioavailability. Thus, the PSD of *rac*-bicalutamide, and in particular, the mean particle diameter, are important parameters to characterize and predict the bioavailability of *rac*-bicalutamide.

The present invention provides *rac*-bicalutamide formulations containing *rac*-bicalutamide having relative small particles and corresponding relatively large surface area.

The present invention provides *rac*-bicalutamide formulations containing *rac*-bicalutamide having a mean particle diameter of less than 200 μm , preferably the mean particle diameter is less than 100 μm , more preferably the mean particle diameter is less than 20 μm , and most preferably the mean particle size is about 10 μm .

The present invention provides *rac*-bicalutamide having a mean particle diameter of between about 200 μm and about 10 μm . In one embodiment of the invention, *rac*-bicalutamide has a mean diameter of about 4.2 μm , more preferably a mean diameter of 4.0 μm .

The present invention also provides process for preparing micronized *rac*-bicalutamide. By the methods of the present invention, *rac*-bicalutamide, which is prepared by methods known in the art, is separated by sieves to produce *rac*-bicalutamide wherein 50% has a mean particle diameter of below about 250 μm and about 80% has a mean particle diameter of below about 500 μm . The sieved *rac*-bicalutamide is then

micronized by methods known in the art, e.g., in a micronizer, to yield *rac*-bicalutamide wherein 100% of *rac*-bicalutamide has a mean particle size of less than about 45 μm , preferably 99% of the *rac*-bicalutamide has a mean particle size of less than about 45 μm , more preferably, 93% of the *rac*-bicalutamide has a mean particle size of less than about 7.5 μm , more preferably the *rac*-bicalutamide isolated has a mean particle diameter of less than about 10 μm .

Micronized particles of *rac*-bicalutamide can be obtained by the use of conventional micronizing techniques after sieving to provide *rac*-bicalutamide wherein about 50% has a particle size of less than about 250 μm and about 80% has a particle size of less than 500 μm . By the methods of the present invention, the *rac*-bicalutamide where about 50% has a particle size less than 500 μm and about 80% has a particle size below about 500 μm , is micronized to the desired particle size range by methods known in the art, for example, using a ball mill, ultraonic means, fluid energy attrition mills, or using a jet mill, or other suitable means as disclosed in Pharmaceutical Dosage Forms: Tablets, Vol. 2, 2nd Ed., Lieberman et al. Ed., Marcel Dekker, Inc. New York (1990) p.107-200, the content of which is incorporated by reference herein.

The present invention provides micronized *rac*-bicalutamide as pharmaceutical compositions that are particularly useful for its anti-androgen activity. Such compositions comprise micronized *rac*-bicalutamide with pharmaceutically acceptable carriers and/or excipients known to one of skilled in the art.

Preferably, these compositions are prepared as medicaments to be administered orally or intravenously. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups and suspensions. While one of ordinary skill in the art will understand that dosages will vary according to the indication, age and severity of the disease of the patient etc., generally micronized *rac*-bicalutamide of the present invention will be administered at a daily dosage of about 2 mg to about 200 mg per day, and preferably about 5 mg to about 100 mg per day.

WHAT IS CLAIMED IS:

1. A *rac*-bicalutamide intermediate having the chemical structure of [X], wherein [X] is a stable organo lithium salt of 4-fluorophenyl methyl sulfone.
- 5 2. A process of preparing a *rac*-bicalutamide intermediate having the chemical structure of [X], comprising the steps of:
 - a) dissolving 4-fluorophenyl methyl sulfone in an organic solvent; and
 - b) adding butyl lithium to the solution, wherein butyl lithium reacts with 4-fluorophenyl methyl sulfone to form [X].
- 10 3. The process according to claim 2, wherein the organic solvent is selected from the group consisting of tetrahydrofuran and diethyl ether.
4. The process according to claim 2, wherein the reaction between butyl lithium with
15 4-fluorophenyl methyl sulfone occurs in the presence of an anion stabilizer.
5. The process according to claim 4, wherein the anion stabilizer is 1,4-diazabicyclo[2.2.2]octane.
- 20 6. The process according to claim 2, wherein the reaction between butyl lithium with 4-fluorophenyl methyl sulfone occurs in a temperature range between about -40°C to about $+10^{\circ}\text{C}$.
7. The process according to claim 2, wherein the reaction between butyl lithium with
25 4-fluorophenyl methyl sulfone occurs in a temperature range between about -2°C and about $+2^{\circ}\text{C}$.
8. A process of preparing ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionate, comprises the steps of:
 - 30 a) preparing a mixture of 4-fluorophenyl methyl sulfone and butyl lithium in an organic solvent;
 - b) adding ethyl pyruvate; and

c) recovering ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionate.

9. The process according to claim 8, wherein the organic solvent is tetrahydrofuran.
- 5 10. The process according to claim 8, wherein the ethyl pyruvate is added to the mixture at a temperature of about -65°C .
11. The process according to claim 8, wherein the recovering step comprises evaporating the mixture containing ethyl pyruvate.
- 10 12. The process according to claim 8, wherein the recovering step further comprises separating the ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionate.
13. A *rac*-bicalutamide intermediate having the chemical structure of [Y], wherein
15 [Y] is a stable organo lithium salt of 5-amino-2-cyano-benzotrifluoride.
14. A process of preparing a *rac*-bicalutamide intermediate having the chemical structure of [Y], comprising the steps of:
- 20 a) dissolving 5-amino-2-cyano-benzotrifluoride in an organic solvent; and
b) adding butyl lithium to the solution, wherein butyl lithium reacts with 5-amino-2-cyano-benzotrifluoride to form [Y].
15. The process according to claim 14, wherein the organic solvent is selected from the group consisting of tetrahydrofuran and diethyl ether.
- 25 16. The process according to claim 14, wherein the reaction between butyl lithium with 5-amino-2-cyano-benzotrifluoride occurs in the presence of an anion stabilizer.
- 30 17. The process according to claim 16, wherein the anion stabilizer is 1,4 diazabicyclo[2.2.2]octane.

18. The process according to claim 14, wherein the reaction between butyl lithium with 5-amino-2-cyano-benzotrifluoride occurs in a temperature range between about -40°C to about $+10^{\circ}\text{C}$.
- 5 19. The process according to claim 14, wherein the reaction between butyl lithium with 5-amino-2-cyano-benzotrifluoride occurs in a temperature range between about -2°C and about $+2^{\circ}\text{C}$.
20. A process of preparing *rac*-bicalutamide, comprising the steps of:
- 10 a) preparing a mixture of 5-amino-2-cyano-benzotrifluoride and butyl lithium in an organic solvent;
- b) adding ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid to the mixture; and
- c) recovering *rac*-bicalutamide.
- 15 21. The process according to claim 20, wherein the organic solvent is selected from the group consisting of tetrahydrofuran and diethyl ether.
22. The process according to claim 20, wherein the ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid is added to the mixture at a temperature of about -65°C .
- 20 23. The process according to claim 20, wherein recovering step comprises evaporating the mixture containing ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid.
- 25 24. The process according to claim 20, wherein the recovering step further comprises separating the ethyl-[2-{4-fluorophenyl sulfone}]-2-hydroxy propionic acid.
- 30 25. The process according to claim 20, wherein the *rac*-bicalutamide is an R-isomer.
26. The process according to claim 20, wherein the *rac*-bicalutamide is an S-isomer.

27. A process of preparing methyl 1,2-epoxy-2-methyl propionate, comprising the steps of:
- a) dissolving oxone in a basic solution;
 - 5 b) adding methyl methacrylate to the oxone solution;
 - c) adding an acid to the oxone solution to form methyl 1,2-epoxy-2-methyl propionate; and
 - d) recovering methyl 1,2-epoxy-2-methyl propionate.
- 10 28. The process according to claim 27, wherein the basic solution is selected from the group consisting of potassium hydroxide and sodium hydroxide.
29. The process according to claim 28, wherein the potassium hydroxide has a concentration of 10 M.
- 15 30. The process according to claim 27, wherein the oxone is 50% KHSO_5 .
31. The process according to claim 27, wherein the methyl methacrylate is added in methanol.
- 20 32. The process according to claim 27, wherein the oxone solution containing methyl methacrylate is maintained at about pH 6.
33. The process according to claim 27, wherein the acid is selected from the group consisting of hydrochloric acid, nitric acid and phosphoric acid.
- 25 34. The process according to claim 33, wherein the hydrochloric acid has a concentration of about 0.05 N to about 5 N.
- 30 35. A process of preparing 2-hydroxy-2-methyl-3-(4-fluorophenylthio) propionic acid, comprising the steps of:
- a) preparing a solution of 4-fluorothiophenol in methanol;

- b) adding methyl-1,2-epoxy-2-methyl propionate to form a mixture;
- c) adding ethyl acetate to the mixture; and
- d) recovering 2-hydroxy-2-methyl-3-(4-fluorophenylthio) propionic acid.

- 5 36. The process according to claim 35, wherein the preparation of 4-fluorothiophenol solution is performed by adding a basic solution under N₂ flow.
37. The process according to claim 36, wherein the basic solution is selected from the group consisting of sodium hydroxide and potassium hydroxide.
- 10 38. The process according to claim 37, wherein the sodium hydroxide has a concentration of 2 N.
39. The process according to claim 35, wherein the mixture is formed by stirring.
- 15 40. The process according to claim 39, wherein the stirring is performed at room temperature for 90 minutes.
41. The process according to claim 35, wherein the recovering step is extraction.
- 20 42. The process according to claim 41, wherein the extraction is achieved by chloroform.
43. The process according to claim 35, wherein the recovering step further involves solidifying 2-hydroxy-2-methyl-3-(4-fluorophenylthio) propionic acid.
- 25 44. A micronized *rac*-bicalutamide, wherein the micronized *rac*-bicalutamide has a mean particle diameter of less than about 200 μm.
- 30 45. A micronized *rac*-bicalutamide, wherein the micronized *rac*-bicalutamide has a mean particle diameter of less than about 100 μm.

46. A micronized *rac*-bicalutamide, wherein the micronized *rac*-bicalutamide has a mean particle diameter of less than 10 μm .
47. A micronized *rac*-bicalutamide, wherein the micronized *rac*-bicalutamide has a mean particle diameter between about 200 μm to about 10 μm .
48. A pharmaceutical composition of *rac*-bicalutamide comprising a micronized *rac*-bicalutamide and a pharmaceutically acceptable salt.
49. The pharmaceutical composition of *rac*-bicalutamide wherein the micronized *rac*-bicalutamide has a mean particle diameter between about 200 μm to about 10 μm .

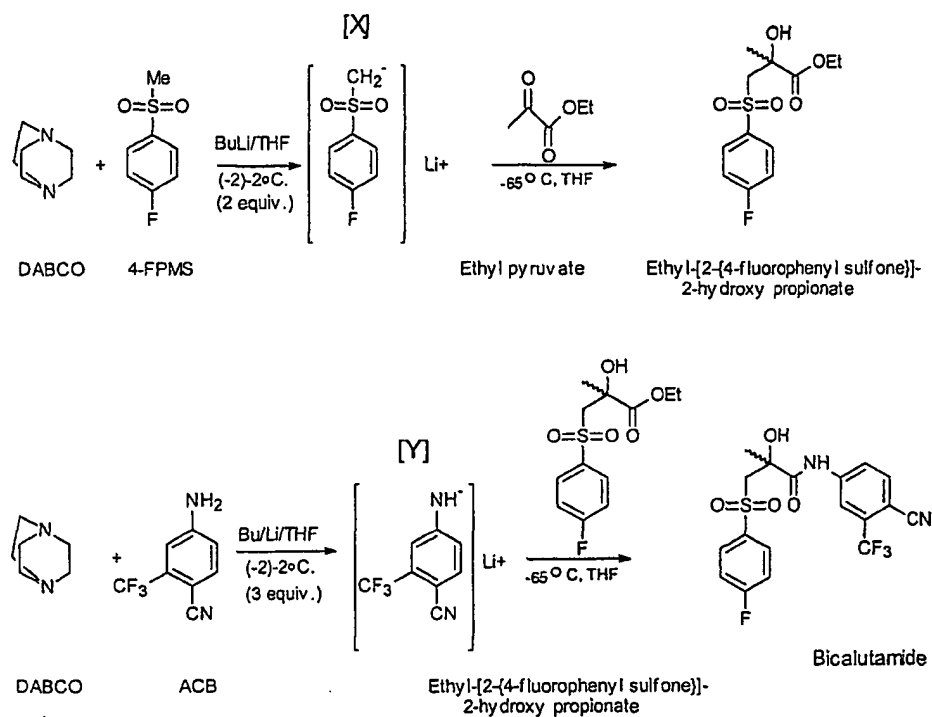


Figure 1

Figure 1: Reaction Pathway of *rac*-Bicalutamide Synthesis Starting From Ethyl Pyruvate.

The abbreviations used are: DABCO: 1,4 diazabicyclo[2.2.2]octane; 4-FPMS: 4-fluorophenyl methyl sulfone; ACB: 5-amino-2-cyano-benzotrifluoride; THF: tetrahydrofuran; and BCL: *rac*-bicalutamide.

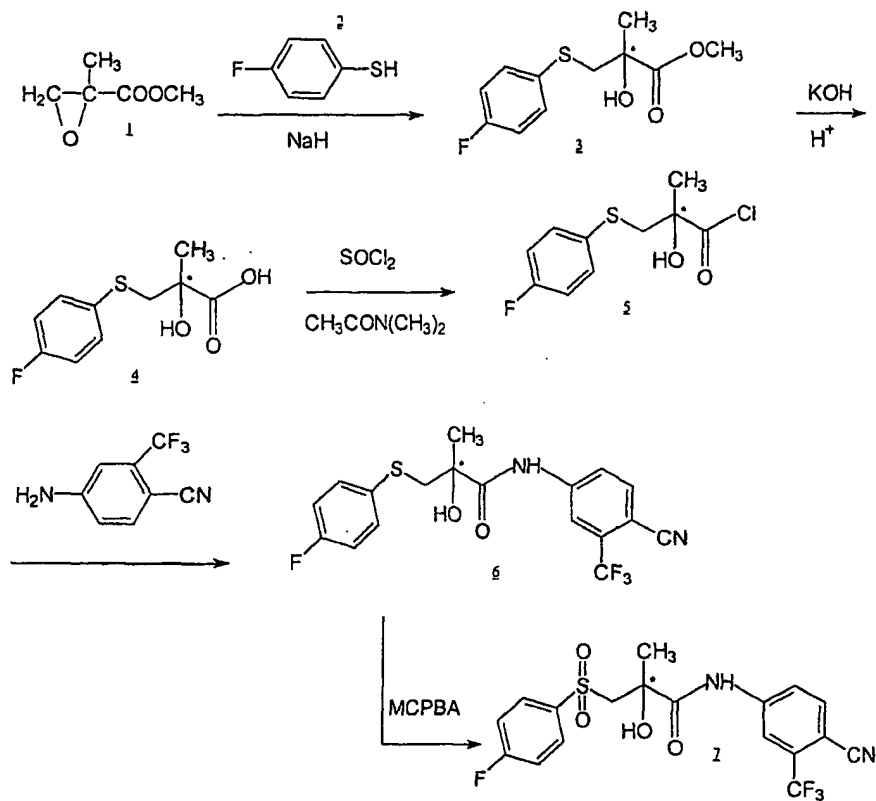


Figure 2

Bicalutamide

Figure 2: Reaction Pathway of *rac*-Bicalutamide Synthesis Starting From Methyl Methacrylate.